
Genetics

Patterns of inheritance

Single gene "Mendelian" Inheritance

- It describes those conditions where single mutant genes have a large effect on human health.
- Pedigree analysis is essential to determine the mode of inheritance of many traits.

Definitions

- **Gene:** the hereditary factor that interacts with the environment to determine a trait.
- **Alleles:** alternative forms of both normal and abnormal genes.
- **Locus:-** is the physical location of the gene on a chromosome.
- **Genotype:-** The genetic constitution of the individual.
- **Phenotype:** The end result of both the genetic & environmental factors giving the clinical picture or the observed expression of the gene.
- **Homozygous:-** The condition of having identical alleles at one locus; which can be either normal or abnormal.
- **Heterozygous:-** The condition of having different alleles at one locus.
- **Dominant condition:-** Evident in both homozygous & heterozygous.
- **Recessive condition:-** Present only in homozygous state.
- **Autosomal:-** It is gene is located on autosomal chromosome.
- **Sex-linked:-** It is genes are located on (X) or / Y chromosome.
- **Compound heterozygous:-** An individual with 2 mutant alleles (different) at one locus.
- **Double heterozygous:-** an individual with 2 mutant alleles that are each at different locus.

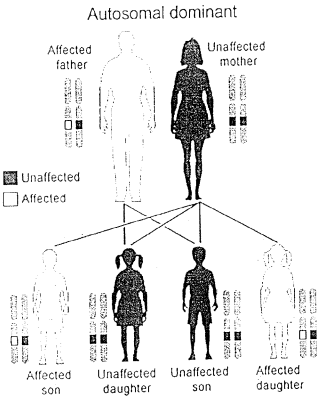
Autosomal Dominant "AD"

Characters

1. One of the parents must be affected.
2. The patient may be homozygous or heterozygous.
3. Unaffected persons are phenotypically normal and genotypically normal.
4. No sex difference.
5. The parents might be clinically free in the following situations:
   - New mutation.
   - Variable expression of the gene.
   - Gene penetrance i.e. The disease might skip one or more generation e.g. disease in grandfather skip the father & reappear in his son.

Examples:

1. Achondroplasia.
2. Osteogenesis imperfecta tarda.
3. Osteopetrosis "Marble bone disease".
4. Spherocytosis & Elliptocytosis.
5. Neurofibromatosis and Huntington chorea.



Autosomal Recessive "AR"

Character

1. Both parents are carriers or one is diseased & the other is carrier.
2. The affected person should be homozygous.
3. Unaffected persons (*phenotypically normal*) are either *genotypically normal or are carriors* (Heterozygous).
4. *Consanguinity* between parents is usually present.
5. *Both sexes* are equally affected.

Examples:

A-IEM:

1. Galactosemia
2. Phenylketonuria "PKU"
3. MSUD (maple syrup urine disease)

4. MPS.

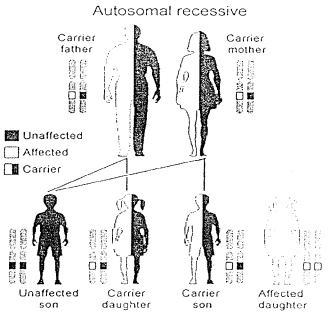
B- Blood:

1- Thalassemia

2- Sickle cell

C. Neurological:

1- Friedreich ataxia



X-Linked Recessive "XLR"

Characters

1. Common in males.
2. Affected father transmits the gene to all his daughters but never his sons.
3. A carrier mother will transmit the character to half of her sons *"Diseased"* & half of her daughters *"carries"*.

4-Free mother = Free offspring.

5- *Females are affected:*

a. Diseased father & Carrier mother

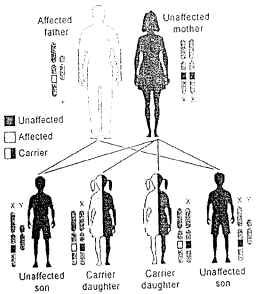
b. Both parents are diseased

c. Turner "XO"

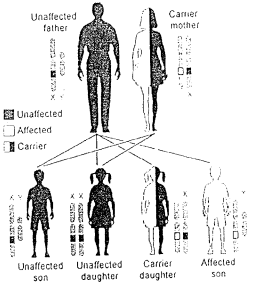
d. New mutation in a carrier female.

e. Lyon's theory in carrier female.

X-linked recessive, affected father



X-linked recessive, carrier mother



Examples:

A. *Blood*

Hemophilia A&B

G-6-PD deficiency

B. *Neurological*

Duchenne myopathy

X- Linked Dominant "XLD"

Characters:

1-Affected father

- Females All are Diseased
- Males All are Free

2-Affected mother "Homozygous"

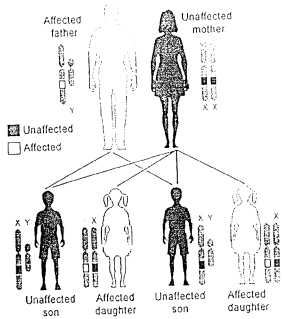
- Females All are Diseased
- Males All are Diseased

3- The clinical Picture is more severe in females than males

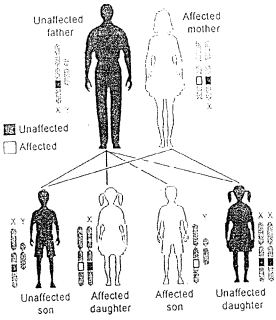
Examples:

Vit-D resistant rickets "1ry hypo - phosphatemic type"

X-linked dominant, affected father



X-linked dominant, affected mother



Y-Linked Inheritance "Holanderic"

Characters:

1- Males are only affected.
2- Father transmit the gene to his Sons

Examples:

Hairy ear pinna

Germ-line mosaicism

In this condition parents are phenotypically normal by all known tests, but in which more than one of their offspring have been affected.

CO-dominance

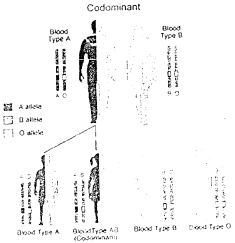
The 2 genes are dominant but not identical
e.g. ABO groups

Intermediate Inheritance

In which the heterozygote differs from individuals homozygous for the mutant allele.

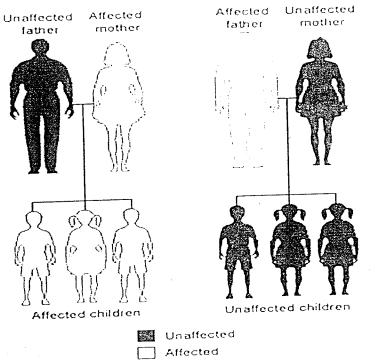
Genetic Heterogeneity

The same phenotype for different genotype.



Mitochondrial inheritance

- Cells have hundreds of mitochondria dispersed throughout the cytoplasm, each containing a number of circular DNA are known to account for a small number of genetic conditions
- It is transmitted from mother to her offspring.



Multifactorial Inheritance

- These are traits that are due to the combination of many genetic (polygenic) and non-genetic factors. Genes and environmental factors affecting a given multi-factorial trait may vary among different individuals. Quantitative traits exhibit continuous variability.
- Qualitative traits follow multi-factorial threshold model, according to which all of an individuals genetic and environmental disease producing factors together, constitute liability which if exceeds a certain threshold the disease occurs.
- Some factors have to be considered in the multi-factorial inheritance model including ; sex, biological relation, consanguinity, concordance state and severity of the trait.
- Heretability is a measure of a proportion of the total variation in character (trait) attributable to genetic factors.

Sex-Chromatin

The human chromosomal structures are composed of 46 chromosomes (female is 46,XX & male is 46, XY).

Q: How to differentiate between male & female cells?

Barr body

If the cell contains more than one X-chromosome , the extra-chromosomes are found to form a deeply stained mass near the nucleus "Barr body"

Thus:

1. Normal male (XY) ⇒ Barr body -ve "chromatin-ve"
2. Normal female (XX) ⇒ Barr body +ve
3. Turner syndrome (XO) ⇒ Barr body -ve
4. Klinefelter (XXY) ⇒ Barr body +ve
5. Super-female (XXX) ⇒ 2 Barr bodies

Drum-Stick

It's present in PMNL & corresponds to the barr body of other cells.
The extra-chromosome attains "Drum stick shape"

Fluorescent body

By using a special fluorescent dye the Y-chromosome. Can be stained & seen under the microscope.

Karyotyping

Will show the exact character of the chromosomes.

Chromosomal Aberration

Etiology

1. Old maternal age
2. Viral infections
3. Irradiations
4. Drugs
5. Certain genes may predispose to chromosomal aberrations. e.g. Gene for fragile X-chromosome predisposes to breaks in the chromosome X.
6. Some chromosomal aberrations predispose to another aberrations e.g. mother with BTC predisposes to translocation Mongol in her offspring.

Mechanisms

I- Non -disjunction

Failure of separation of the 2 homologous chromosomes or chromatids during the anaphase ⇒ formation of 2-daughter cells

- One with extra-chromosome (24 chromosome).
- One with less-chromosome (22 chromosome)

II- Breakage

Apart of the chromosome is broken with the result of

1-Deletion

The broken part is lost

2- Translocation

The broken part is joined to another chromosome.

3- Inversion

The broken part in inverted & re-united to the same chromosome

4-Ring chromosome

The 2 terminal parts of chromosome are broken & the two terminal ends unite together forming a ring.

III. Iso- chromosome formation

Instead of longitudinal division of one chromosome to form 2 separate chromatids it divides at the centromere transversely to form 2 non-identical parts:

- One formed of 2 short arms
- One formed of 2 long arms

Each of them is called iso-chromosome

TYPES OF CHROMOSOMAL ABERRATION

I. Numerical chromosomal aberrations

II. Structural chromosomal aberrations

I. Numerical chromosomal aberrations

An-euploidy	Poly-ploidy
- The number of chromosomes is not exactly the duplicate of 23. -It's either 47 chromosome "*Trisomy*" or 45 chromosome "Monosomy". -Monosomy is not compatible with life except in case of Turner syndrome "45,X"	- The number of chromosomes is the multiple of 23 i.e. 3x23, 4x23...etc. -All these anomalies are incompatible with life & are usually found in abortions. -*Triploidy* : is due to fertilization by 2 sperms. -*Tetraploidy* : is due to failure to complete the 1st zygotic division.

Examples:

1- *Trisomy of autosomal chromosomes*
Trisomy 2l, 18, 13

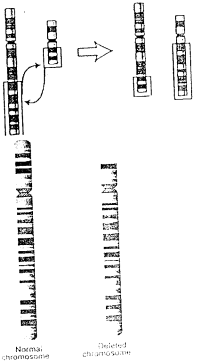
2- *Trisomy of sex chromosomes*
Klinefelter (XXY)
Super female (XXX)
Supper male (XYY)

3-*Monosomy of X-chromosome*
Turner syndrome (XO).

B-Structural **Chromosomal** aberrations

I-Translocation:

- Apart of chromosome or the whole chromosome is translocated to another chromosome *Balanced Translocation Carrier "BTC"*
- During gametogenesis, the faulty arrangement of chromosomes *Unbalanced Translocation*.



II- Deletion:

Simple breakage of one chromosomes with loss of small part of it

e.g. 1- Cri-du-Chait syndrome ($5p^-$)

2- ($4p^-$) syndrome

3- Deletion of X-chromosome (Turner)

Mongolism (Down syndrome)

Due to presence of an extra 21 chromosome

Incidence:

1/700 live births.
The incidence at conception is greater but more than 60 % are spontaneously aborted and at least 20 % are stillborn

Cytogenetic types:

I. Non -disjunction Mongol "95%"

- It's caused by failure of separation of the two chromosomes no.21 during meiosis ⇒ formation of an ovum containing an extra-21 chromosome.
- It's an age dependent type, the older the maternal age, the more common the incidence.
- The Karyotyping of the baby is 47 with an extra-21 chromosome
- The mother has a normal Karyotyping 46
- It's the most common type "95%"
- The risk increases with age , about 1 in 200 for a 36 years old mother rising to 1 in 100 at 39 years and 1 in 50 at 42 years.

II. Translocation Mongol "4%"

In this type the extra 21 chromosome is translocated to another chromosomes:-

- To chromosome 14 (the most common).
- To chromosome 15
- To chromosome 13
- To chromosome 22
- To chromosome 21 ⇒ the most serious prognosis why?

The mother

Is a BTC, with a Karyotyping of 45 chromosome + translocation of 21 chromosome to another chromosome. While the Mongol is 46 chromosome + translocation

Theoretically

The recurrence risk in case of translocation of 21 to 13,14,15,22 is 1/3 of the living births.

However
The true recurrence risk is about 10-15 % "if the mother is a BTC"
while 2% if the father is a BTC .....why?
In case of translocation 21 to 21 the risk is 100 % (the worst prognosis)

III. Mosaic Mongol: (1 %)

See before (mentality is less affected).

CLINICAL PICTURE

I. Mental deficiency

Presenting as delayed milestones of development

II. Growth retardation

Presenting as delayed growth" wt & height"

III. Characteristic physical signs

A. Head manifestations:

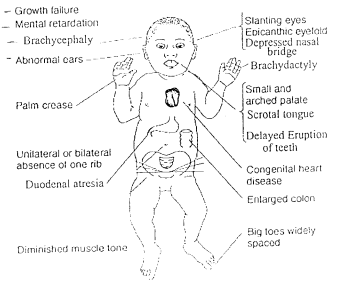
Delayed closure of The anterior fontanel & fine silky hair

- Depressed Nasal bridge.
- Brachy cephaly.
- Medial epicanthic fold.
- Narrow palpebral fissure.
- Upward slanting Eyes.
- Apparent squint .
- Brush field iris.
- Retro-micrognathia.
- Delayed Eruption of teeth& small oral cavit
- Scrotal tongue (protruded fissured tongue).



B. Limb manifestations:-

- Inclino-dactyly (the little finger is incurved inward& has single crease due to rudimentary middle phalanx
- Brachydactyly (short fingers)
- Single crease in the palmar aspect (simian crease) complete or partial
- Big space between 1st & 2nd toes



IV. Hypotonia:

- Marked laxity of the ligaments (Acrobatic sign).
- Viscero-ptosis.
- Pot-belly abdomen.
- Umbilical hernia.

V. Auto-immune diseases

- Hashimoto thyroiditis

Management

a. Genetic counseling

1- A mother who is over 35 years ,with normal children then gets a Mongol ⇒ mostly non-disjunction

So the possibility to get another Mongol is Low but still higher than younger mother

2- A young mother who gets a Mongol with history of repeated abortions ⇒ mostly the mother is BTC

Do Karyotyping

21 Translocation to 14,13,15,22 → 1/3 of live-born will be Mongol

21 Translocation to 21 → 100% of living children will be Mongol

So:

Amniocentesis & Karyotyping of the amniotic fluid is indicated in

1. Pregnant women over 35 years
2. Mothers known to be BTC
3. Mothers with a history of birth of a Mongol.

Treatment

There's no specific curative treatment the aim is

1. Treatment of associated congenital anomalies & infections.
2. General nutritional, hygienic & medical care.
3. Special social, educational & behavioral therapy in specialized institute.

Anti-mongolism

It's caused by deletion of long arm of chromosome 21

CLINICAL PICTURE

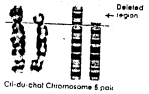
1. MR
2. Growth retardation
3. Microcephaly
4. Congenital anomalies as
   - Hypospedius & cryptorchidism
   - Pyloric stenosis & inguinal hernia
   - Micrognathia & high arched palate.
   - Skeletal & nail anomalies.

In contrast to Mongol there are

i. Hypertonia.
ii. Downward slating eyes.
iii. Prominent nasal Bridge.
iv. Big ears.

Cri-du-chat syndrome

Due to deletion of short arm of chromosome no.5 (5P-)



CLINICAL PICTURE

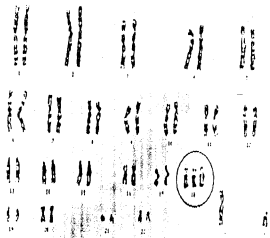
- MR
- Growth retardation
- Microcephaly
- Congenital heart disease
- Marked hypertelorism
- Cat-like cry due to laryngeal hypoplasia
- Rounded face.



Trisomy 18 "T18" (Edwards)

Incidence

1 / 3000 live births
Male / Female ratio =1/3 because there is increase spontaneous abortion in male fetus



CLINICAL PICTURE

- MR
- Growth Retardation
- Microcephaly
- Congenital heart disease
- Micrognathia
- Short sternum & narrow pelvis
- Hernias: inguinal & umbilical.

Characteristic features:

1. Hypertonia.
2. Prominent occiput.
3. Low set malformed ears.
4. Clinched fist.
5. Rocker bottom heel.



Death frequently in early infancy or early childhood due to multiple congenital anomalies or pneumonia (only 10 % survive beyond 1st year).

Treatment

1- General supportive care
2- Genetic counseling.

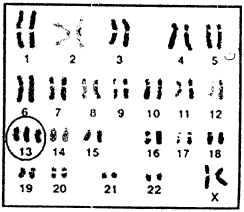
Trisomy 13

Incidence

1/ 5000 of live births

Clinical Picture

- MR
- Growth retardation
- Microcephaly
- Congenital heart disease "VSD"
- Midline facial defects :
  - Absent nose
  - Single nostril (cebocephaly).
  - Single eye (cyclopia).
  - Microphthalmia
  - Cataract
  - Anophthalmia
  - Coloboma.
  - Cleft lip / palate
- Polydactyly
- Low set ears
- Umbilical hernia
- Cryptorchidism
- Rocker bottom heals
- Capillary hemangiomas





Treatment

1- supportive care

Turner Syndrome "45,XO"

Incidence

1 / 5000 of living female newborns

Spontaneous abortion occurs in 95% of affected pregnancies & only 5% are born alive.

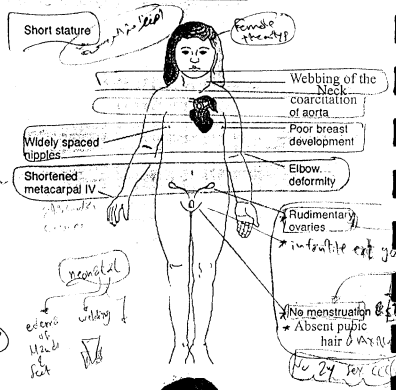
Clinical Picture

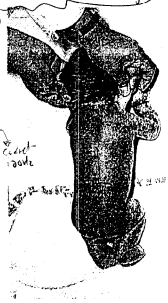
Female phenotype.

- Short stature
- Webbing of the neck
- Coarcitation of the aorta
- Widely spaced nipple.
- Absent or minimal axillary hair
- Breast is not developed
- Cubitus valgus
- Wide carrying angle
- Absent or minimal pubic hair
- Infantile external genitalia
- 1ry amenorrhea & sterility
- Streaked atrophic gonads

In the neonatal period

- Webbing of the neck
- Triangular face
- Coarcitation of aorta
- Edema of hands & feet "non Pitting"







Widely spaced nipple in Turner

Investigations

1. ↑↑ Serum pituitary gonadotropins ,FSH & LH.
2. ↓↓↓ Serum level of female sex hormones esp. Estrogens
3. Buccal smear → Barr body.
4. Karyotyping

May show one of the following

- Monosomy -X (45,XO) (common)
- Mosaicism 45,XO /46,XX
- Iso-chromosome of the long arm of one X-chromosome (2 long arms with no short arms)

Deletion of short arm
Short stature
Turner phenotype
But no ovarian dysfunction
Deletion of long arm
Failure of ovarian development.

Treatment

GH then Estrogen replacement therapy

1- Help development of 2ry sexual character
2- Permit normal menses
3- Prevent development of osteoporosis

During pregnancy Turner syndrome may present with generalized edema (Hydrops) or localized nuchal swelling which may be mistaken on ultrasonography as encephalocele. This is due to delayed maturation of the lymphatic system.

Klinefelter Syndrome (47,XXY)

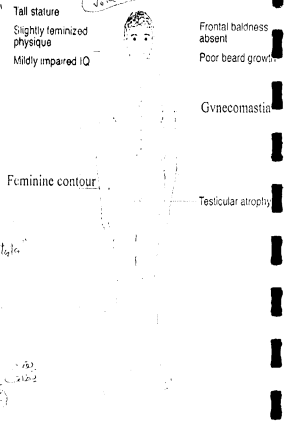
Incidence

- 1/1000 of living newborn males
- It's associated with old maternal age.

Clinical Picture

Characteristic Feature do not appeal- till after age of puberty

- Male phenotype
- *Tall stature* due to marked delay in epiphyseal closure (Androgens)
- *Gynecomastia* & feminine contour of the body
- *Small atrophic testes*
- *Failure of 2ry sexual characters* to develop e.g. mustache, beard, axillary & pubic hairs in addition to small penis . The voice does not become harsh.
- *Sterility* & *Impotence* with lack of libido
- Mentality may be affected, especially with more than 2 X chromosomes.



Investigations

1. ↑↑↑Pituitary gonadotropins (LH & FSH)
2. ↓↓↓Male sex hormones (testosterone)
3. Buccal smear ⇒ Barr body +ve
4. Testicular biopsy ⇒ Hyalinization & atrophy
5. Karyotyping may show one of the following
   a. 47 ,XXY in the majority of patients
   b. Rare variants ⇒ 48 ,XXY, 49,XXXX
   c. Mosaics ⇒ 46,XY & 47,XXY(some)

Treatment

Testosterone replacement therapy

Super-male (47XYY)

- This syndrome presents in 10% of tall men (taller than 180 cm) with defective aggressive personality ,which may lead to conflicts with law
- Abnormal behavioral pattern is usually present since childhood.

Mentality ⇒ may be slightly affected.

Fertility ⇒ may be normal

Fragile -X Syndrome

- It account for more than 30- 50 % of cases of X-linked mental deficiency in males & 10% of cases of MR in females
- It's caused by spontaneous breaks of the long arm of X- chromosome.
- This syndrome is inherited in an X-linked recessive manner.

Clinical Picture

1. MR: more severe in males
2. Oblong face with large ears & prominent jaw
3. Markedly big testes in affected males esp. after puberty with normal size of penis.
4. In childhood, autism & convulsions may occur.

Investigations

Karyotyping Using a special technique, the fragile part at the end of long arm of X-chromosome can be demonstrated.

Super-female (47,XXX)

Clinical Picture

1. MR: more severe with more X-chromosome.
2. Tall stature.
3. All her children will be normal.

Q: What are the indications of Karyotyping?

Indications of Karyotyping

1. Confirmation of suspected diagnosis of chromosomal etiology.
2. Persons with multiple congenital anomalies.
3. Mothers of repeated spontaneous abortion
4. Female with 1^{ry} amenorrhea or sterility
5. Abnormal external genitalia
6. All persons with MR of unknown cause.
7. Ambiguous genitalia
8. Female with short stature of unknown etiology
9. Pregnant mother over 35 years.
10. Mothers with BTC
11. History of previous child with chromosomal abnormality.